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09/210,747	12/15/1998	ROBERT E BRIGGS	0029577957	4952

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EXAMINER
PORTNER, VIRGINIA ALLEN

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

File Copy

Office Action Summary	Application No. 09/210,747	Applicant(s) Briggs et al
	Examiner Portner	Art Unit 1645

-- The MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jul 2, 2003* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *40-44, 48, 49, and 57-66* is/are pending in the application.

4a) Of the above, claim(s) *63-66* is/are withdrawn from consideration.

5) ☒ Claim(s) *40-44* is/are allowed.

6) ☒ Claim(s) *48, 49, and 57-62* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☒ Claims *40-44, 48, 49, and 57-66* are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 23
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-39, 45-47, 50-56 have been canceled.

Claims 40-44,48-49, 57-62 and 63-66 are pending.

Claims 40-44 are allowed; claims 48-49 and 57-62 are under consideration.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Allowable Subject Matter

2. Claims 40-44, upon processing the terminal disclaimer submitted April 7, 2000 and it being found proper define over the prior art of record.

Election/Restriction

3. Newly submitted claims 63-66 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: All previously examined claims did not recite any specific structural mutation, but functionally defined the mutation to attenuate the claimed P.haemolytica in the recited gene. The newly submitted claims are directed to deletion mutations, and deletion mutant strains produced by a series of process steps not previously examined for each of the leukotoxin B gene, thus defining specific species of invention that are independent and distinct from the compositions previously examined on the merits. The vaccines of claims 63-66 structurally differ from the compositions previously examined, therefore defining compositions that differ by structure, function and biological effect.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 63-66 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Rejections Withdrawn

4. Claims 47, 55-56 rejected under 35 U.S.C. 102(b) as being anticipated by Ricketts et al (Third International Veterinary Immunology Symposium Budapest, Hungary, August 17-20 1992, abstract PS7.19), in light of the claims having been canceled.

Rejections Maintained

5. Claims 48-49, 57-62 rejected under 35 U.S.C. 112, first paragraph (scope of enablement for vaccine compositions), because the specification, does not provide enablement for Pasteurella haemolytica vaccines that comprise any mutations in the leukotoxin C, A, B or D genes and the use of these strains as a vaccine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the claimed inventions, and to use them as vaccines for reasons of record in paper number 16, as applied to claims 46-47, paragraph 9 and for reasons of record in paper number 19, paragraphs 9-13.

6. Claims 48-49 and 57-62 (new claims) rejected under 35 U.S.C. 112, first paragraph (*written description)*, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had *possession* of the claimed invention, for the same reasons as applied to claims 48-49, made of in paper number 16, paragraph 10; and for reasons of record in paper number 19, paragraphs 9-13.

7. Claims 48-49 are rejected under 35 U.S.C. 102(b) as being anticipated by Chidambaram et al (May 1992, B-143) as evidenced by Chidambaram et al (1995, Infection and Immunity).

Response to Arguments

8. The rejection of claims 48-49, 57-62 under 35 U.S.C. 112, first paragraph (scope of enablement for vaccine compositions), because the specification, does not provide enablement for Pasteurella haemolytica vaccines that comprise any mutations in the leukotoxin C, A, B or D genes and the use of these strains as a vaccine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the claimed inventions, and to use them as vaccine is traversed on the grounds:

a. The prior art does not disclose the claimed vaccines; and the examiner "acknowledges that the subject matter of claims 48,49 and 57-62 is novel over the prior art"; and

b. Chidambaram II is not prior art to the present application and the fact that "the authors of Chidambaram II were apparently unaware of the teachings of Applicants' 1993 specification does not negate the enablement provided in the instant specification.

9. In response to the above arguments, it is the position of the examiner that the instant specification does not provide any added knowledge to the knowledge that is generally known in vaccine art of Pasteurella haemolytica vaccines with mutations in a leukotoxin genes or leukotoxin A, B, C or D open reading frames. Applicant's instant specification does not provide guidance as to where in the leukotoxin genes the mutations must or can be made to produce a mutant strain of Pasteurella haemolytica that would result in a mutant strain that would function as a vaccine strain. Critical sequence regions the must be preserved or disrupted in order to attain the desired leukotoxin mutant strain that functions as a vaccine are not disclosed or described.

The instant specification, page 7, lines 11-12 states:

"[O]ther genes in which mutations may be desirable are genes in the leukotoxin operon (C,A, B, D)". The specification only mentions leukotoxin genes briefly in passing. The statement made is in the future tense "may be desirable". This statement does not teach, nor provide guidance for the production of vaccine mutant strains that comprise a leukotoxin gene mutations. The phrase "may be desirable" clearly defines a future desire, at most a suggestion but without guidance, and shows that Applicant did not have possession of the claimed vaccine strains at the time of filing as suggestion is contemplative.

Clearly the instant specification has enabled embodiments (claims 40-44 have been indicated as allowable), but claims 48-49, 57-62 have not been enabled as vaccines compositions (compositions that induce a strong immune response are not automatically vaccines (see Boslego,page 212, column 2, paragraphs 2 and 5, last sentences, "no protective effect" and "afforded no protection against experimental gonorrhea"), as the vaccine art is unpredictable, references were provided by the examiner to show Pasteurella haemolytica vaccines are not predictable, the claimed compositions have not been described and therefore not enabled.

10. With respect to Chidambaram et al (1995) not being prior art; the agrees this reference is not prior art, but in an enablement rejection, references cited under 35 U.S.C. 112, first paragraph need not be made public prior to Applicant's filing date. Any evidence may be used to show lack of enablement regardless of the date of publication.

Chidambaram et al (1995) was cited by the examiner because the reference shows unpredictability in the production of mutant strains of Pasteurella haemolytica. Chidambaram et al teaches "[S]ince no mutagenesis procedure had been published previously for P.haemolytica, it was first necessary to establish a mutagenesis protocol. (See page 1028, col. 2, paragraph 4)" Problems existed in the art of Pasteurella haemolytica mutagenesis because this bacterium carries a prophage that is induced by many DNA-damaging treatments (Richards et al, Am. J. Vet. Res., Vol.46, pages 1215-1220, 1985). Thus, any mutagen that was used should avoid prophage induction." Production of mutant strains of Pasteurella haemolytica is taught to be complicated and thus unpredictable due to the presence of a prophage induced by treatment of P.haemolytica DNA with a mutagen. The instant specification does not teach any specific method or protocol to prevent the induction of P.haemolytica's prophage; prophage activation would preclude the production of a living mutant strain of P.haemolytica. Chidambaram et al (1995) also teach that "genetic mapping is not yet possible for P.haemolytica (see page 1030, col. 1, paragraph 3).

The claimed invention is directed to any type mutant strain, as long as some degree of over all attenuation of the cell is accomplished. The leukotoxin expressed or not expressed by the mutant Pasteurella must result in an attenuated mutant. The leukotoxin operon is not required to be deleted, or completely inactivated; the mutation must only result in some degree of attenuation.

The instantly claimed genus claims directed to Pasteurella haemolytica mutant bacterium with a mutation in a leukotoxin A gene, leukotoxin B gene, leukotoxin D gene or leukotoxin C gene, does not evidence a "reasonable correlation between the disclosure and the scope of the claim" because no guidance, direction, sequences, or showing of induction of a Protective immune response with a leukotoxin gene mutant has been disclosed, and this type of vaccine is

Not generally known in the prior art . The instant specification provides only a probable suggestion. Arguments set forth in paper number 19, paragraphs 9-13 are incorporated herein by reference, as well as discussion and arguments set forth in paper number 21, pages 3-13 with respect to 35 U.S.C. 112, first paragraph.

11. Applicant requests clarification how the phrase "genetic mapping is not yet possible for P.haemolytica" at page 11, of the Amendment paragraph 2, shows lack of enablement of the instantly claimed invention.

12. In response to Applicant's request for clarification with respect to the importance of understanding genetic organization (genetic mapping) and gene sequences of the a species of bacteria into which a mutation is introduce in order to obtain a vaccine mutant strain, the examiner cited Davies et al (Journal of Bacteriology, Vol. 183 and Vol. 184) who teaches that the leukotoxin operon evidences many structural allelic variations (see Vol. 183, pages 1394-1403), is highly polymorphic with multiple alleles (see Vol. 184, page 267, col. 1, paragraph 2), and production of a mutant strain would require knowledge of where the genes are located in the specific Pasteurella haemolytica strains, and what the coding sequences are for the genes, in order to introduce the desired mutation to produce a leukotoxin mutant strain of Pasteurella haemolytica that is attenuated. The instant specification is lacking in this disclosure and guidance in order to obtain the instantly claimed vaccines strains of leukotoxin mutant strains of Pasteurella haemolytica.

Additionally, Davies et al (Vol. 183, page 1396, Table 1) shows that there are at least 14 different coding sequences for leukotoxin A, with variations in nucleotide and amino acid sequence from 1.0 to 17 % (see Vol. 183, page 1397, Table 2 and page 1399, Figure 3); teaches that there are 12 different leukotoxin C coding sequences (see Vol. 184, page 269, col. 2,

paragraph 3;Vol. 183, figure 2, page 270), 19 different leukotoxin B sequences (see Vol. 183, figure 3, page 270) and 11 different leukotoxin D sequences (see Vol. 183, figure 4, page 271). None of these leukotoxin gene sequences have been described, nor has any guidance has been provided in the instant specification as to where or how the instantly claimed genus of leukotoxin gene mutant strains of Pasteurella haemolytica could be made and highly variable sequence for these genes was not generally known in the art at the time of filing of the instant specification.

The evidence cited was relevant to the production of mutant leukotoxin genes in Pasteurella haemolytica and the utilization of compositions as vaccines, wherein the evidence showed and provided insight into the unpredictability of Pasteurella vaccines, variability in genetic make up between strains of Pasteurella haemolytica so one method would not necessarily to applicable to all strains of Pasteurella haemolytica (Davies et al), and the existence of prophage carrying strains of Pasteurella haemolytica that would preclude the production of living mutant strains without activation of the prophage which would result in cell death.

13. Applicant asserts that "[T]he Office has not met its burden of providing acceptable evidence or reasoning to support a prima facie case of non-enablement and of giving proper weight to the evidence of record."

14. It is the position of the examiner that sufficient evidence has been provided to establish a prima facie case of lack of enablement over the SCOPE of the instantly claimed invention which is directed to Pasteurella haemolytica leukotoxin mutant vaccine compositions and the examiner has also provided evidence and arguments with respect to the lack of written description rejection under 35 US 112, first paragraph, wherein the instant specification does not "reasonably convey to one skilled in the relevant art that the inventor(s), at the time of the application was filed, had possession of the claimed invention which is directed to mutant leukotoxin C, A, B or D stains of Pasteurella haemolytica that would serve as vaccine strains.

The scope of enablement rejection over claims 48-49, 57-62, directed to leukotoxin mutant vaccines strains of Pasteurella haemolytica was also set forth because no speicific mutations in the leukotoxin genes had been described, that would serve to produce and induce a protective immune response when the mutant leukotoxin genes of Pasteurella haemolytica were present in a mutant strain of Pasteurella haemolytica had been disclosed. The scope of enablement rejection is maintained for reasons of record in paper number 21.

15. The rejection of claims 48-49 under 35 U.S.C. 102(b) as being anticipated by Chidambaram et al (May 1992, B-143) as evidenced by Chidambaram et al (1995, Infection and Immunity) is traversed on the grounds that:

Mutations in the leukotoxin B or D genes would not be responsible for such a phenotype as disclosed in "Chidambaram I" which was cited as inherently disclosing "two mutant strains...".

16. It is the position of the examiner that leukotoxin B and leukotoxin D genes are associated with secretion of leukotoxin (Swiss-Prot) and the mutant Pasteurella haemolytica mutant strains did not secret leukotoxin "[T]here was no leukotoxin visible in the supernatant of the two mutants (abstract lines 8-9) as well as were lacking in leukotoxin production (see line 3 of abstract).

17. Applicant asserts that leukotoxin B or D genes would not be responsible for a phenotype that is leukotoxin production negative.

18. It is the position of the Examiner that without secretion, a leukotoxin positive phenotype would not be established. With a mutation in the leukotoxin operon prior to the leukotoxin B or D open reading frames (see page 1031, Chidambaram et al 1995 Figure 6 showing the leukotoxin operon organization), which would prevent transcription and/or translation of leukotoxin B or D gene products, no leukotoxin would be secreted, and a leukotoxin negative phenotype would be assigned. Both mutant Pasteurella haemolytica strains were leukotoxin negative, as no leukotoxin products were secreted, nor detected in the sample. A mutation in the leukotoxin operon, and not necessarily in the leukotoxin B or D open reading frames would be considered to a mutation in

the leukotoxin B gene or the leukotoxin D gene, which function as a unit within the leukotoxin operon of Pasteurella haemolytica. Arguments directed to claims withdrawn from consideration will not be addressed as the claims have not been examined (specifically claims 63-66).

19. Chidambaram II is traversed as not being extrinsic evidence that the strains of Chidambaram I (1992) are inherently leukotoxin B or D mutant strains of Pasteurella haemolytica.
20. It is the position of the examiner the 1995 Chidambaram et al reference provides evidence for the organization of the leukotoxin operon organization (see 1995 reference, page 1031, Figure 6 for diagram of leukotoxin operon used by Chidambaram et al). a mutation that would result in a secretion negative (leukotoxin B or D mutant) mutant strain of Pasteurella haemolytica would be a mutant strain with mutation in the leukotoxin B and D genes, and Chidambaram et al (1992) disclosed secretion negative strains of Chidambaram I (1992).

The 1992 abstract sets forth two strains which are leukotoxin mutants, which are leukotoxin negative. The strains did not secrete any leukotoxin in the supernatant and therefore comprise a mutation effecting the leukotoxin B and D genes which are secretion genes. a mutation in the operon prior to the leukotoxin B or D open reading frames (in the operon initiation region (promoter), in leukotoxin orf a or C) would cause an error in transcription/translation and expression of a leukotoxin positive phenotype and define a leukotoxin B or D mutant strain; also a mutation in the leukotoxin B open reading frame (orf) would cause a mutation in the leukotoxin B and D genes as a reading frame error would effect both leukotoxin orf B and D.

As the mutation recited in the claims 48-49 and 57-62 may be any type of mutation that causes a mutation in the leukotoxin B or D genes (not limited to the leukotoxin open reading frame but reads on the entire operon that effects expression of the leukotoxin B and D proteins that are associated with secretion of leukotoxin), the mutants of Chidambaram et al (1992) which did not secret any leukotoxin comprise a mutation that is in the leukotoxin operon, thus a

mutation in the leukotoxin B and D genes (see abstract lines 3-4). The rejection is maintained for reasons of record.

Conclusion

21. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

a shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be Group Art Unit 1645. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to this Art Unit.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

vgp
September 2, 2003

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